

IT IS CLAIMED:

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A¹₅
1. A method of synthesizing a plurality of compounds, comprising:
 - (a) forming a first group of subsets of nucleic acid tags, where the nucleic acid tags in each subset each has a selected one of a plurality of different first hybridization sequences, a mixture of different second hybridization sequences, and a chemical reaction site,
 - (b) reacting the chemical reaction sites in each of the subsets formed in (a) with a selected reagent, thereby to form a reagent-specific compound intermediate on the associated sequence in each subset,
 - 10 (c) forming a second group of subsets of the reacted nucleic acid tags, where the tags in each subset each have a selected one of a plurality of different second hybridization sequences, and a mixture of different first hybridization sequences; and
 - (d) reacting the compound intermediates in the sequences in each of the subsets formed in (c) with a selected reagent.
 2. The method of claim 1, wherein each of said forming steps includes hybridizing the nucleic acid tags within a given subset with a plurality of solid phase reagents each having a surface bound oligonucleotide or oligonucleotide analog capable of forming base-specific duplexes with one of the hybridizing sequences in the given subset to bind each nucleic acid tag to one of the reagents.
 3. The method of claim 1, for use in forming a plurality of oligomers with different subunit sequences, wherein each of said reacting steps includes adding a selected subunit to each of the subsets of nucleic acid tags under conditions effective to add that subunit to the chemical reaction site or last-added subunit carried thereon.
 - 25 4. The method of claim 1, for use in forming a plurality of small molecules with different chemical sequences, wherein each of said reacting steps includes adding a selected chemical substituent to each of the subsets of nucleic acid tags under conditions effective to add that substituent to the chemical reaction site or last-added substituent carried thereon.
 - 30 5. The method of claim 1 for making a plurality of compounds requiring more than 2 synthetic steps wherein the nucleic acid tags include an additional step-specific subset of hybridization sequences for each synthetic step greater than 2 and which further comprises, for each additional synthetic step;

(e) forming groups of subsets of reacted nucleic acid tags, wherein the sequences in each subset each have a selected one of a plurality of hybridization sequences in a step-specific subset of nucleic acid tags, and a mixture of different other hybridization sequences;

(f) reacting the compound intermediates in the sequences in each of the subsets formed in (e) with a selected reagent; and

(g) repeating steps (e) and (f) if necessary, until synthesis of the compounds is complete.

6. The method of claim 1 or 5 wherein each subset of nucleic acid tags includes at least 5 separate hybridization sequences.

7. The method of claim 1, wherein said nucleic acid tags within each subset further comprises for each subset of hybridization sequences, an adjacent spacer sequence separating that hybridization sequence from an adjacent one, each of said spacer sequences being the same for all subsets of nucleic acid tags and each hybridization sequence being different for each group of subsets of nucleic acid tags.

8. The method according to claim 1, for use in enriching the plurality of compounds in those having a desired compound activity, further comprising identifying from said plurality of compounds, one or more compounds having a desired activity to yield a subpopulation of nucleic acid tags, and using the subpopulation to carry out the method of claim 1.

9. The method according to claim 8, wherein said using includes;
amplifying said subpopulation of nucleic acid tags by non-specific polymerase chain reaction (PCR),
adding a chemical reaction site, and
using said amplified subpopulation having chemical reaction sites to carry out the method of claim 1.

10. The method according to claim 9, for use in producing new permutations of active compounds wherein said nucleic acid tags have one of a plurality of spacer sequences, each of said spacer sequences having a unique restriction enzyme site;

(e) identifying from said plurality of compounds, one or more compounds having a desired activity to yield a subpopulation of nucleic acid tags;

(f) treating said subpopulation of nucleic acid tags with

one or more restriction enzymes under conditions effective to produce a partial digest;

(g) rejoining said partially digested nucleic acid tags;

(h) adding a new chemical reaction site to said partially digested nucleic acid tags and using the subpopulation to carry out the method of ~~claim~~ 1.

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11. A library of nucleic acid tags for use in directing the synthesis of a plurality of compounds comprising a first segment having a selected one of a plurality of different first hybridization sequences, a second segment having a selected one of a plurality of different second hybridization sequences and a chemical reaction site wherein said first and second hybridization sequences are non-
10 hybridizing with one another.

12. The library of nucleic acid tags according to ~~claim~~ 11, wherein said hybridization sequences are at least 10 nucleotides long.

13. The library of nucleic acid tags according to ~~claim~~ 11, for making a plurality of compounds requiring more than 2 synthetic steps wherein the nucleic acid sequences include an additional step-specific segment of hybridization sequences for each synthetic step greater than 2, wherein each sequence has a selected one of a plurality of hybridization sequences and said hybridization sequences are non-hybridizing with one another.

14. A combinatorial library of compounds, each combinatorial compound comprising a nucleic acid tag having a first segment with a selected one of a plurality of different first hybridization sequences, a second segment having a selected one of a plurality of different second hybridization sequences and a chemical reaction site wherein said first and second hybridization sequences are non-
20 hybridizing with one another, and a compound formed on said chemical reaction site by step-wise chemical reaction which is directed by the associated nucleic acid tag.